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(54) Title: COMBINATIONS OF VANILLOID COMPOUNDS AND PHOSPHONATE ANTIVIRAL COMPOUNDS FOR TREATMENT OF HERPES INFECTIONS

(57) Abstract

The subject invention involves methods of treating or preventing lesion epidodes in humans, due to *Herpes* infections, comprising administering to the human a combination of a vanilloid compound and a phosphonate antiviral compound.

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+ DESIGNATIONS OF "SU"

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COMBINATIONS OF VANILLOID COMPOUNDS AND PHOSPHONATE ANTIVIRAL COMPOUNDS FOR TREATMENT OF HERPES INFECTIONS

TECHNICAL FIELD

The subject invention relates to a novel method for the treatment of Herpes infections.

BACKGROUND OF THE INVENTION

The subject invention involves natural and synthetic vanilloid compounds. The following references disclose vanilloid compounds and are incorporated herein by reference: U.S. Patent No. 4,313,958 issued to LaHann on February 2, 1982; U.S. Patent No. 4,401,663 issued to Buckwalter & LaHann on August 30, 1983; U.S. Patent 4,424,205 issued to LaHann & Buckwalter on January 3, 1984; U.S. Patent No. 4,443,473 issued to Buckwalter & LaHann on April 17, 1984; U.S. Patent No. 4,460,602 issued to Buckwalter & LaHann on July 17, 1984; U.S. Patent No. 4,493,848 issued to LaHann & Buckwalter on January 15, 1985; U.S. Patent No. 4,532,139 issued to Janusz & LaHann on July 30, 1985; U.S. Patent No. 4,544,668 issued to Janusz, Buckwalter & LaHann on October 1, 1985; U.S. Patent No. 4,544,669 issued to LaHann, Janusz & Buckwalter on October 1, 1985; U.S. Patent No. 4,564,633 issued to LaHann & Buckwalter on January 14, 1986; U.S. Patent 4,898,887 issued to Janusz, Loomans, LaHann & Kasting, on February 6, 1990; U.S. Patent Application Serial No. 473,122 of Berman, Buckwalter, Cupps & Gardner, filed January 31, 1990; U.S. Patent Application Serial No. 404,924 of Gardner, Kasting, Cupps, Echler, Gibson & Shulman, filed September 8, 1989; U.S. Patent No. 4,810,716 issued to Connor & Flynn on March 7, 1989; U.K. Patent Application No. 2,168,974A of Loomans & Buckwalter, published July 2, 1986; U.K. Patent Application No. 2,168,975A of Janusz & Loomans, published July 2, 1986; and U.K. Patent Application No. 2,168,976 A of Loomans, Janusz & Buckwalter, published July 2, 1986; U.K. Patent Application No. 2,206,347A of Masdin, Walpole & Wrigglesworth, published January 5, 1989; and PCT Patent

Application No. WO 89/04297 of Johnson & Rafferty published May 18, 1989.

Vanilloid compounds have been generally disclosed in the above references to have analgesic, anti-irritant and anti-inflammatory activity. Vanilloid compounds have been disclosed to be useful in the treatment of Herpes simplex infections in European Patent Application No. 0,347,000 of O'Neill, Kasting & Cupps, published December 20, 1989.

The subject invention also involves phosphonate antiviral compounds. Certain phosphonate antiviral compounds have been disclosed to have anti-herpetic activity. Phosphonate antiviral compounds are disclosed in the following references which are incorporated herein by reference: U.S. Patent No. 3,767,795 issued to Schleicher & Roderick on October 23, 1973; U.S. Patent No. 4,016,264 issued to Clark on April 5, 1977; U.S. Patent No. 4,052,439 issued to Herrin & Fairgrieve on October 4, 1977; U.S. Patent No. 4,056,673 issued to Heimer & Nussbaum on November 1, 1977; U.S. Patent No. 4,087,522 issued to Von Esch on May 2, 1978; U.S. Patent No. 4,092,412 issued to Mao, Seely & Fairgrieve on May 30, 1978; U.S. Patent No. 4,150,125 issued to Herrin & Fairgrieve on April 17, 1979; U.S. Patent No. 4,182,759 issued to Diana on January 8, 1980; U.S. Patent No. 4,215,113 issued to Eriksson, Helgstrand, Misiorny, Stening & Stridh on July 29, 1980; U.S. Patent No. 4,217,346 issued to Diana on August 12, 1980; U.S. Patent No. 4,272,528 issued to Von Esch, Thomas, Fairgrieve & Seely on June 9, 1981; U.S. Patent No. 4,340,599 issued to Lieb, Oediger & Streible on July 20, 1082; U.S. Patent No. 4,372,894 issued to Helgstrand, Johannson, Misiorny, Norén & Stening on February 8, 1983; U.S. Patent No. 4,386,081 issued to Helgstrand, Johansson, Misiorny, Norén & Stening on May 31, 1983; U.S. Patent No. 4,536,400 issued to Helgstrand, Johansson, Misiorny, Norén & Stening on August 20, 1985; U.S. Patent No. 4,591,583 issued to Helgstrand, Misiorny, Norén & Stening on May 27, 1986; U.S. Patent No. 4,665,062 issued to Eriksson, Helgstrand, Misiorny, Stening & Stridh on May 12, 1987; U.S. Patent No. 4,771,041 issued to Eriksson, Helgstrand, Misiorny, Stening & Str on September 13, 1988; and Diana, G.D., E.S. Zalay,

U.J. Salvador, F. Pancic & B. Steinberg, "Synthesis of Some Phosphonates with Antiherpetic Activity", Journal of Medicinal Chemistry, Vol. 27 (1984), pp. 691-694.

Herpes Zoster Infections

Herpes zoster infections are caused by the varicella-zoster virus (VZV), the etiologic agent of the conditions commonly known as shingles, zona and acute posterior ganglionitis.

VZV lesion episodes usually cause severe pain and exhibit large groups of lesions distributed along the course of a sensory nerve. The vesicular eruptions of Herpes zoster are often activated by systemic diseases such as Hodgkins, and immunosuppressive therapy.

VZV is also the causative agent in chicken pox. Later Herpes zoster infections (or shingles outbreaks) are most common after the age of fifty. Crops of vesicles form on an erythemateous base and follow the sensory distribution of one or more posterior root ganglia. The sensory zone on the skin that is affected is usually hyperalgesic with associated severe pain.

Herpes zoster lesion episodes rarely recur in a patient (recurrence rate is less than 2%); one attack, generally associated with an outbreak of lesions in any one of numerous areas of the skin surface, usually confers immunity thereafter.

Herpes Simplex Infections

Clinically, Herpes zoster infections may have some similarity to Herpes simplex virus (HSV) infections, but several important differences between the two exist.

Herpes simplex lesion episodes are characterized by generalized or localized cutaneous and mucosal lesions, often with associated severe constitutional (general, not local) symptoms. The virus spreads along sensory nerves and becomes established in the regional sensory ganglia, or area of neuron cell bodies. HSV usually present with latent infections in the trigeminal or presacral ganglia (Type I) or dorsal root ganglia (Type II). Although VZV infections generally produce latent infections, these occur mainly in the dorsal root ganglia.

HSV infections are generally of two types, Type I or Type II. Type I HSV infections are mainly implicated in oral or

ocular Herpes infections. HSV Type II infections are usually genital and transmitted primarily through direct contact with Herpes lesions. While Herpes simplex lesions may appear anywhere on the skin or mucosa, they most frequently appear on the mouth, the lips, the conjunctiva and cornea and the genitalia.

Unlike the 2% recurrence rate of VZV lesion episodes, the likelihood of Type I HSV recurrence is 80%, while the likelihood of Type II HSV recurrence is 50%. Reinfection with different strains of Type II HSV may also occur. Recurrent herpetic eruptions can be precipitated by conditions as broad as over exposure to sunlight, febrile illness, physical or emotional stress, or certain foods or drugs.

The primary lesions of HSV (vesicular eruptions) are the most painful, prolonged and widespread. During periods of vesicular eruption, patients often experience pain in the region of viral infection. This pain, though it may be severe, resolves upon healing of the herpetic lesions, and leaves the patient basically asymptomatic between recurrent herpetic episodes.

OBJECTS OF THE PRESENT INVENTION

It is an object of the present invention to provide new methods which are effective for treating or preventing lesion episodes due to Herpes infections.

It is a further object of the present invention to provide methods for preventing or reducing the severity of recurrent lesion episodes due to Herpes simplex infections.

SUMMARY OF THE INVENTION

The subject invention involves methods of treating or preventing lesion epidodes in humans, due to Herpes infections, comprising administering to the humans combinations of vanilloid compounds and phosphonate antiviral compounds.

DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl", as used herein, means carbon-containing chains which may be straight, branched, or cyclic;

substituted or unsubstituted; and which may be saturated, mono-unsaturated (i.e., one double or triple bond in the chain), or polyunsaturated (e.g., two or more double bonds in the chain; two or more triple bonds in the chain; one or more double and one or more triple bonds in the chain). Unless indicated otherwise, alkyl preferences, alone and/or collectively, are as follows. Preferred alkyl are straight or branched chain, especially straight chain. Preferred alkyl are unsubstituted. Preferred alkyl are monounsaturated, or especially saturated. Preferred alkyl are about C_1-C_{20}, more preferably about C_1-C_{10}. Preferred alkyl are lower alkyl, about C_1-C_6, more preferably about C_1-C_4, more preferably still C_1-C_2, especially C_1. Substituted alkyl groups can be mono- or polysubstituted. Preferred is mono-, di- or trisubstituted; more preferred is monosubstituted. Preferred substitutents are selected from the group consisting of halogen, hydroxy, alkoxy, aryloxy, amino, nitro, cyano, trifluoromethyl, thiol, aryl, heteroaryl and carboxylate; more preferred are halogen, hydroxy, amino, thiol, aryl and carboxylate; most preferred are hydroxy or amino, and also aryl.

As used herein, saturated alkyl groups are referred to as "alkanyl"; unsaturated alkyl groups comprising double bonds in the chain are referred to as "alkenyl" (preferred are chains having the double bonds in the "Z" or "cis" geometric configuration); and unsaturated alkyl groups comprising triple bonds in the chain are referred to as "alkynyl". The designation of geometric configurations for any double bonds present in compounds of the present invention utilizes the art-known nomenclature "Z" and "E", and is fully described in Morrison and Boyd, Organic Chemistry, Third Edition (Allyn and Bacon, Inc., Boston; 1973), pp. 131-133 and 148-151; and March, Advanced Organic Chemistry, Second Edition (McGraw-Hill Book Company, New York; 1977), pp. 86-124; the disclosures of both these references being incorporated herein by reference in their entirety.

The terms "aryl" and "heteroaryl", as used herein, mean aryl or heteroaryl rings which may be mono-, di-, or tri-substituted or unsubstituted, preferably monosubstituted or unsubstituted. Additionally, heteroaryl rings comprise at least one heteroatom

in the ring structure. As used herein, "heteroatom" means an atom other than carbon that can covalently bond to at least two other atoms and become part of a stable chemical structure. Preferred heteroatoms are nitrogen, oxygen and sulfur. Preferred aryls and heteroaryls include substituted or unsubstituted phenyl, naphthyl, pyridyl, pyrimidyl, imidazolyl, furanyl, thiophenyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, triazinyl, pyrrolyl, indolyl and purinyl. More preferred aryls and heteroaryls include unsubstituted and substituted phenyl, pyridyl, imidazolyl, furanyl and thiophenyl. Most preferred aryl is unsubstituted or substituted phenyl. Substituted aryls and heteroaryls can be mono- or polysubstituted. Preferred is mono-, di- or trisubstituted; more preferred is monosubstituted. Preferred substituents include halogen, hydroxy, alkoxy, amino, nitro, cyano, phenyl, benzyl, benzyloxy, trifluoromethyl, formylamino, carboxylate and alkyl; more preferred substituents include alkyl, alkoxy, halogen, hydroxy, amino and carboxy; most preferred are halogen, and especially lower alkyl. More preferred aryl or heteroaryl is unsubstituted.

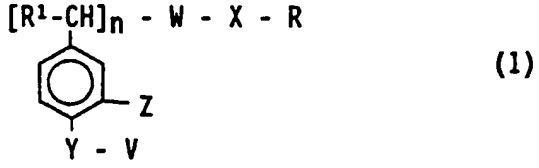
The term "carboxylate", as used herein, means an organic carboxylic acid moiety (i.e., COOH), and the salts (e.g., sodium, potassium, calcium, tetraethylammonium) and esters (e.g., methyl ester, ethyl ester) and amides (e.g., unsubstituted amide, N-methyl amide, N,N-dimethyl amide) thereof.

The term "pharmaceutically-acceptable salts, esters and/or amides", as used herein, means the compounds referred to in their salt or ester or amide form which have the same general pharmacological properties as the basic amino form from which they are derived, and which are acceptable from a toxicity viewpoint. Pharmaceutically-acceptable salts include ammonium salts derived from inorganic acids (e.g., HCl, HBr, $NaHSO_4$, H_2CO_3), and ammonium carboxylic acid salts derived from organic carboxylic acids (e.g., acetic acid; lactic acid; gluconic acid; citric acid; glucuronic acid; galacturonic acid; fumaric acid; gentisic acid; lactobionic acid; benzoic acid). Pharmaceutically-acceptable amides include those derived from organic carboxylic acids (e.g., acetic acid amides) including amino acids (e.g., glycine amides).

The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the components of a pharmaceutical carrier are capable of being commingled with the vanilloid compounds and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the pharmaceutical composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

Vanilloid Compounds and Compositions

The vanilloid compounds useful in the present invention are natural and synthetic vanilloid compounds, and the pharmaceutically-acceptable salts thereof, having the general structure:



(1)

In structure (1) n = 0 or 1.

In structure (1), the -W-X- moiety is selected from -C(O)NH-, -C(S)NH-, $-S(O)_2NH-$, -NHC(O)O-, -NHC(S)O-, -NHC(O)NH-, and -NHC(S)NH-. Preferred -W-X- is selected from -C(O)NH-, -C(S)NH-, -NHC(O)NH-, -NHC(S)NH- and $-S(O)_2NH-$. More preferred -W-X- is selected from -C(O)NH-, -C(S)NH-, and -NHC(O)NH-. Most preferred -W-X- is -C(O)NH-. Either available bond of the -W-X- moiety may be bonded to the -R moiety, with the other bond being attached to the benzyl carbon atom, or directly attached to the benzene ring.

In structure (1), the $-R^1$ moiety is selected from hydrogen, hydroxy, lower alkyl esters of hydroxy, lower alkyl, and lower alkoxy. Preferred $-R^1$ is selected from hydrogen, hydroxy, and methyl; most preferred $-R^1$ is hydrogen.

In structure (1), the -Z moiety is selected from hydrogen, hydroxy and methoxy; preferred -Z is selected from hydroxy and methoxy. Most preferred -Z is methoxy.

In structure (1), the -Y- moiety is selected from -O-, -S-, $-NR^4-$, -OC(O)-, $-OSO_3^-$-, and $-OPO_3^=$-, where $-R^4$ is selected from hydrogen and C_1-C_4 alkanyl; preferred -Y- is selected from -O- , -S- and -NH-. More preferred -Y- is selected from -O- and -S-; most preferred -Y- is -O-.

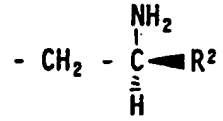
In structure (1) the -V moiety is selected from hydrogen, short chain alkyl, and $-CR^2_2-CR^2_2-NH_2$. Preferred -V is selected from C_1 to C_3 alkyl and hydrogen. Even more preferred -V is selected from hydrogen and methyl, especially hydrogen. Also more preferred is -V being $-CR^2_2-CR^2_2-NH_2$.

The $-R^2$ moieties are each independently selected from hydrogen; halogen; unsubstituted or substituted alkyl, the alkyl portion having from about 1 to about 6 carbon atoms; substituted or unsubstituted aryl or heteroaryl; and carboxylate; or two $-R^2$ moieties are covalently bonded to form a substituted or unsubstituted alkyl, heteroalkyl, aryl or heteroaryl ring having from about 3 to about 8 atoms, preferably 3-6 atoms, in the ring, including from 0 to about 3 heteroatoms. It is preferred that no more than two $-R^2$ are other than hydrogen. Preferred $-R^2$ substituents other than hydrogen include unsubstituted and substituted lower alkyl (preferred substituents being hydroxy, amino and phenyl) and unsubstituted and substituted phenyl. It is preferred that at least one $-R^2$ on the alpha carbon atom (the carbon atom bonded directly to the Y moiety) be a hydrogen. Also preferred is at most only one $-R^2$ being other than hydrogen. Also preferred is all $-R^2$ being hydrogen.

Also preferred is where both $-R^2$ on the alpha carbon atom are hydrogen and both $-R^2$ on the beta carbon atom (the carbon atom bonded directly to the alpha carbon atom) are unsubstituted or substituted alkyl or are covalently bonded to form a substituted or unsubstituted alkyl or heteroalkyl ring having from about 3 to about 8 atoms, including from 0 to about 3 heteroatoms, in the ring. Preferred is a substituted or unsubstituted alkyl ring having from about 3 to about 6 carbon atoms, more

preferably 3 or 4 or 5 carbon atoms in the ring. Preferred -R^2 alkyl moieties on the beta carbon atom are saturated or unsaturated having a single double or triple bond, more preferred is that both -R^2 on the beta carbon be unsubstituted or substituted alkanyl or covalently bonded to form an unsubstituted or substituted alkanyl ring. More preferred still is that both -R^2 on the beta carbon atom are methyl or ethyl, especially methyl.

Also preferred is where both -R^2 on the alpha carbon atom are hydrogen, one -R^2 on the beta carbon atom is hydrogen and the other is arylalkyl or heteroarylalkyl, preferably having the structure -$(CH_2)_n$-Ar, wherein -Ar is aryl or heteroaryl and n is an integer from 1 to about 6; preferably n is 1 or 2, especially 1. Preferred aryl and heteroaryl moieties of this structure include unsubstituted and substituted phenyl, pyridyl, or furanyl, especially unsubstituted and substituted phenyl. Preferred substitutents on the aryl or heteroaryl moiety include chloro, methyl, methoxy, nitro, fluoro, and C_1-C_6 alkyl. Most preferred aryl is phenyl, especially unsubstituted phenyl. In such compounds, the beta carbon is a chiral center; preferred compounds have the S-enantiomer structure: -V being



In structure (1) the -R moiety is a C_1-C_{24} alkyl moiety which may be straight, branched or cyclic chain and may be saturated, monounsaturated, or polyunsaturated, substituted or unsubstituted.

Preferred -R moieties are straight and branched chain alkanyl, straight and branched chain monounsaturated alkyl, straight and branched chain diunsaturated alkyl, and straight and branched chain triunsaturated alkyl. More preferred -R moieties are mono or diunsaturated or saturated, C_6-C_{24} straight or branched chain alkyls. Also more preferred are C_6-C_{14} straight chain alkyls, especially C_7-C_{10} straight chain alkanyls. Even more preferred are mono or diunsaturated alkenyls, or C_6-C_{24} straight chain alkenyls. Further preferred are monounsaturated

cis-double bond C_6-C_{18} straight or branched chain alkenyls. Even further preferred is mono-unsaturated cis-double bond C_8-C_{14} straight chain alkenyls. Such preferred -R moieties are preferably unsubstituted.

Other preferred -R moieties are arylalkyls having a C_1-C_{12}, more preferably C_1-C_6, most preferably C_1-C_2, alkyl portion which is preferably straight chain and also preferably alkanyl. The aryl portion is preferably unsubstituted or substituted phenyl.

Preferred -R groups are selected from n-hexanyl, n-heptanyl, n-octanyl, n-nonanyl, n-decanyl, n-undecanyl, n-dodecanyl, n-tridecanyl, n-tetradecanyl, octenyl, nonenyl, decenyl, undecenyl, dodecenyl, tridecenyl, tetradecenyl, octadienyl, nonadienyl, decadienyl, undecadienyl, dodecadienyl, tridecadienyl and tetradecadienyl. More preferred -R groups are selected from n-octanyl, n-nonanyl, n-decanyl, 7-methyl-5E- or 5Z-octenyl, 9-decenyl, 8Z-undecenyl, 9Z-dodecnyl, 8Z-tridecnyl, and 9Z-tetradecenyl.

Preferred compounds useful in the subject invention include 8-methyl-N-vanillyl-6-nonenamide; N-vanillylnonanamide; N-vanillyl-9-octadecenamide; N-((4-(2-aminoethoxy)-3-methoxyphenyl)-methyl)-9Z-octadecenamide; N-((4-(2-aminoethoxy)-3-methoxyphenyl)-methyl)-nonanamide; N-((4-(2-methyl-2-aminopropoxy)-3-methoxyphenyl)-methyl)-nonanamide; N-((4-(2-methyl-2-aminopropoxy)-3-methoxyphenyl)-methyl)-9Z-octadecenamide; N-((4-(2-amino-3-methylbutoxy)-3-methoxyphenyl)-methyl)-9Z-octadecenamide; N-((4-(1-amino-1-cyclopropylmethoxy)-3-methoxyphenyl)methyl)-9Z-octadecenamide; N-((4-(1-amino-1-cyclopentylmethoxy)-3-methoxy)phenyl)methyl)-9Z-octadecenamide; N-(9Z-octadecenyl)-4-(2-amino-2-methylpropoxy)-3-methoxyphenylacetamide; N-(9Z-octadecenyl)-4-(2-aminoethoxy)-3-methoxyphenylacetamide; N-octanyl-4-(2-aminoethoxy)-3-methoxyphenylacetamide; N-((4-(2-amino-3-hydroxypropoxy)-3-methoxyphenyl)-methyl)-9Z-octadecenamide; N-((4-(2-amino-2-carboxyethoxy)-3-methoxyphenyl)-methyl)-9Z-octadecenamide; N-(9-decenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-dodecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9-decenamide; N-((4-hydroxy-3-

methoxyphenyl)-methyl)-9Z-dodecenamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-tetradecenamide; N-((4-(3-phenyl-2(S)-2-amino-1-propoxy)-3-methoxyphenyl)methyl)-nonanamide; and the pharmaceutically-acceptable salts and amides thereof. More preferred compounds useful in the methods of the present invention include 8-methyl-N-vanillyl-6-nonenamide; N-vanillylnonanamide; N-(9-decenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-dodecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9-decenamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-tetradecenamide; N-((4-(3-phenyl-2(S)-2-amino-1-propoxy)-3-methoxyphenyl)-methyl)-nonanamide; and the pharmaceutically-acceptable salts and amides thereof.

Preferred pharamaceutically-acceptable salts for the vanilloid compounds are the ammonium carboxylic acid salts derived from organic carboxylic acids, especially the acetate and lactate salts.

Specific vanilloid pharmaceutical compositions useful in this invention are described in the following U.S. Patents, all incorporated by reference herein: U.S. Patent No. 4,401,663, Buckwalter, et al, issued August 30, 1983; U.S. Patent No. 4,424,205, LaHann, et al, issued January 31, 1984; U.S. Patent No. 4,443,473, Buckwalter, et al, issued April 12, 1984; U.S. Patent No. 4,493,848, LaHann, et al, issued January 15, 1985. Vanilloid pharmaceutical compositions preferably comprise one or more of the vanilloid compounds and a pharmaceutically-acceptable carrier. Total single dosages of the vanilloid compounds present in pharmaceutical compositions useful herein are generally from about 1 ug to about 1 g. Preferred single dosages are from about 10 ug to about 100 mg; more preferred are from about 100 ug to about 50 mg; and most preferred are from about 1 mg to about 10 mg.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the vanilloid compounds in the subject invention is largely determined by the way the compound is to be

administered. Such methods include parenteral (especially subcutaneous), oral and topical.

Phosphonate Antiviral Compounds and Compositions

As used herein, "phosphonate antiviral compounds" include antiviral compounds which are phosphonate derivatives.

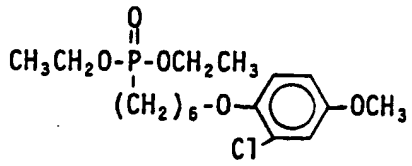
Preferred phosphonate antiviral compounds useful in the subject invention are derivatives of phosphonoacetic acid. Examples of "phosphonoacetic acid antiviral compounds" are disclosed in U.S. Patent Nos. 3,767,795, 4,016,264, 4,052,439, 4,056,673, 4,087,522, 4,092,412, 4,272,528 and 4,340,599, which have been incorporated herein by reference.

Preferred phosphonate antiviral compounds useful in the subject invention also include phosphonoformic acid and derivatives thereof. Examples of "phosphonoformate antiviral compounds" are disclosed in U.S. Patent Nos. 4,215,113, 4,372,894, 4,386,081, 4,536,400, 4,591,583, 4,665,062 and 4,771,041, which have been incorporated herein by reference.

The phosphonoformate antiviral compounds useful in the subject invention include those disclosed in U.S. Patent No. 4,215,113 issued to Erickson, Helgstrand, Mizyorni, Stenning and Strigg on July 29, 1980, being phosphonoformic acid and physiologically-acceptable salts thereof. Suitable salts include, for example, amine salts, such as dimethylamine, triethylamine, ammonium, tetrabutylammonium, cyclohexylamine and dicyclohexylamine; and metal salts, such as mono-, di- and trisodium, mono-, di- and tripotassium, magnesium, calcium and zinc. The most preferred compound is foscarnet, the trisodium salt of phosphonoformic acid.

Phosphonate antiviral compounds include other phosphonate derivatives having antiviral activity. Examples of other phosphonate antiviral compounds are arylalkyl and aryloxyalkyl phosphonates disclosed in U.S. Patent Nos. 4,182,759 and 4,217,346, which have been incorporated herein by reference.

A preferred aryloxyalkylphosphonate is fosarilate having the structure:



Methods of Treating Herpes Simplex Infections

The subject invention involves methods of treating Herpes infections, particularly methods of alleviating signs and symptoms associated with herpetic vesicular eruptions and the attendant pain of Herpes lesions by administering to a person a safe and effective amount of a combination of a vanilloid compound and a phosphonate antiviral compound. The methods of the subject invention include the prevention of recurrent Herpes simplex lesion episodes and/or the reduction in number and/or severity of Herpes simplex or Herpes zoster vesicular eruptions that manifest in a lesion episode.

The phrase a "safe and effective amount", as used herein, means an amount of compounds or compositions high enough to significantly positively modify the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. The safe and effective amount of compounds or compositions will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific compounds or compositions employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

The vanilloid compounds and the phosphonate antiviral compounds useful in the subject invention may be administered to a person together in a single composition or separately in different compositions. When administered separately in different compositions, the compounds may be administered by the same or different routes of administration, and may be administered at about the same time or at different times.

Daily dosages of vanilloid compounds preferably range from about 0.01 mg/kg of body weight to about 200 mg/kg of body weight. More preferred daily dosages are from about 0.1 mg/kg to about 10 mg/kg of body weight; still more preferred daily dosages are from about 0.2 mg/kg to about 1 mg/kg of body weight. Up to about 6, preferably from about 1 to about 4, single dosages per day may be administered.

Preferred routes of administration of vanilloid compounds include topical, peroral, and parenteral; more preferred are topical and peroral; most preferred is topical. Topical administration can be used by directly laying on or spreading a safe and effective amount of a vanilloid composition on epidermal or epithelial tissue, including outer skin and oral, anal, vaginal and gingival tissue. The amount of the pharmaceutical composition to be topically administered may vary from about 1 mg/cm^2 to about 20 mg/cm^2, and if a patch is worn over the affected area possibly higher amounts, depending upon such factors as the sensitivity, type and location of tissue to be treated, the composition and carrier to be administered, and the particular compound to be administered.

When administered topically, the vanilloid compound is preferably administered between lesion episodes to tissue in areas where lesions previously occurred and/or are likely to occur, especially on the face or in the genital region. The vanilloid compound is preferably administered topically for from about 1 to about 60 days at a frequency of about weekly to about yearly, more preferably for from about 2 days to about 30 days at a frequency of from about biweekly to about twice yearly, more preferably still for from about 3 days to about 15 days at a frequency of from about monthly to about thrice yearly, most preferably from about 4 days to about 7 days at a frequency of from about bimonthly to about trimonthly. On days when the vanilloid compound is administered topically, it is preferably administered from about once to about six times daily, more preferably from about twice to about 4 times daily.

Preferred routes of administration of phosphonate antiviral compounds are peroral, topical, and parenteral (especially

intravenous); preferred routes of administration are peroral and topical, especially peroral.

Daily dosages of phosphonate antiviral compounds preferably range from about 0.01 mg/kg of body weight to about 20 mg/kg of body weight. More preferred daily dosages are from about 0.1 mg/kg to about 15 mg/kg of body weight; still more preferred daily dosages are from about 1 mg/kg to about 10 mg/kg of body weight; more preferably still from about 5 mg/kg to about 8 mg/kg of body weight. Up to about 8, preferably from about 1 to about 6, more preferably from about 2 to about 4, single dosages per day may be administered. The phosphonate antiviral compound is preferably administered everyday, although less frequent administration is often effective.

An animal model which can be used to demonstrate the use of combinations of vanilloid compounds and phosphonate antiviral compounds for the prevention or treatment of lesion episodes of Herpes simplex infections is disclosed in Stanberry, L.R., R. L. Burke and M. G. Myers, "Herpes Simplex Virus Glycoprotein Treatment of Recurrent Genital Herpes", The Journal of Infectious Diseases, Vol. 157, (1988), pp. 156-163; and Stanberry, L. R., S. Kit and M. G. Myers, "Thymidine Kinase-deficient Herpes Simplex Virus Type 2 Genital Infection in Guinea Pigs", Journal of Virology, Vol. 55, (1985), pp. 322-328.

Combination Compositions

The subject invention also includes pharmaceutical compositions comprising one or more vanilloid compounds, one or more phosphonate antiviral compounds, and a pharamaceutically-acceptable carrier. Preferred combination compositions of the subject invention comprise one vanilloid compound, one phosphonate antiviral compound and a carrier formulated for topical, peroral or parenteral administration. Preferred combination compositions of the subject invention are for topical administration.

As used herein, "administered topically" means placing the compounds, whether vanilloid, phosphonate antiviral, or combinations thereof, in contact with the skin, mucous membrane, or body cavity. It thus includes epidermal, intraoral, intravaginal, intraanal, and intraaural administration. Preferred methods of

the subject invention involve topical administration of one or both of the active compounds. Suitable pharmaceutically-acceptable carriers for topical application include those suited for use in lotions, creams, solutions, gels, ointments, tapes and the like.

Suitable carriers for topical administration preferably remain in place on the skin as a continuous film and resist being washed off easily by perspiration or by immersion in water. Generally, the carrier is either organic in nature or an aqueous emulsion and capable of having the vanilloid compound dispersed or dissolved therein. The carrier may include pharmaceutically-acceptable emollients, skin penetration enhancers, coloring agents, fragrances, emulsifiers, thickening agents, and solvents. A more detailed description of such forms follows:

Suitable carriers for topical administration preferably remain in place on the skin as a continuous film and resist being washed off easily by perspiration or by immersion in water. Generally, the carrier is either organic in nature or an aqueous emulsion and capable of having the vanilloid compound dispersed or dissolved therein. The carrier may include pharmaceutically-acceptable emollients, skin penetration enhancers, coloring agents, fragrances, emulsifiers, thickening agents, and solvents. A more detailed description of such forms follows:

1. Lotions

The lotions can comprise an effective amount (preferably from about 0.001% to about 5%, more preferably from about 0.1% to about 1%) of a vanilloid compound; from 1% to 50%, preferably from 3% to 15%, of an emollient; the balance being water, a C_2 or C_3 alcohol, or a mixture of water and the alcohol. Several emollients are known. Examples of such emollients are as follows:

a. Hydrocarbon oils and waxes. Examples are mineral oil, petrolatum, paraffin, ceresin, ozokerite, microcrystalline wax, polyethylene, and perhydrosqualene.

b. Silicone oils, such as dimethylpolysiloxanes, methylphenylpolysiloxanes, water-soluble and alcohol-soluble silcone-glycol copolymers.

c. Triglyceride fats and oils such as those derived from vegetable, animal and marine sources. Examples include castor oil, safflower oil, cotton seed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, and soybean oil.

d. Acetoglyceride esters, such as acetylated monoglycerides.

e. Ethoxylated glycerides, such as ethoxylated glyceryl monostearate.

f. Alkyl esters of fatty acids having 10 to 20 carbon atoms. Methyl, isopropyl and butyl esters of fatty acids are useful herein. Examples include hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, isopropyl myristate, decyl oleate, isodecyl oleate, hexadecyl stearate, decyl stearate, isopropyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate.

g. Alkenyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include oleyl myristate, oleyl stearate, and oleyl oleate.

h. Fatty acids having 9 to 22 carbon atoms. Suitable examples include pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidonic, behenic, and erucic acids.

i. Fatty alcohols having 10 to 22 carbon atoms. Lauryl, myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, erucyl, and 2-octyl dodecyl alcohols are examples of satisfactory fatty alcohols.

j. Fatty alcohol ethers. Ethoxylated fatty alcohols of 10 to 20 carbon atoms include the lauryl, cetyl, stearyl, isostearyl, oleyl, and cholesterol alcohols having attached thereto from 1 to 50 ethylene oxide groups or 1 to 50 propylene oxide groups, or a mixture thereof.

k. Ether-esters such as fatty acid esters of ethoxylated fatty alcohols.

l. Lanolin and derivatives. Lanolin, lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate,

ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin alcohols, acetylated lanolin, acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of ethoxylated alcohols-esters, hydrogenolysis of lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin absorption bases are illustrative of emollients derived from lanolin.

m. Polyhydric alcohols and polyether derivatives. Propylene glycol, dipropylene glycol, polypropylene glycol (M.W. 2000-4000), polyoxyethylene polyoxypropylene glycols, polyoxypropylene polyoxyethylene glycols, glycerol, ethoxylated glycerol, propoxylated glycerol, sorbitol, ethoxylated sorbitol, hydroxypropyl sorbitol, polyethylene glycol (M.W. 200-6000), methoxy polyethylene glycols 350, 550,750, 2000, 5000, poly[ethylene oxide] homopolymers (M.W. 100,000-5,000,000), polyalkylene glycols and derivatives, hexylene glycol (2-methyl-2,4-pentanediol), 1,3-butylene glycol, 1,2,6-hexanetriol, ethohexadiol USP (2-ethyl-1,3-hexanediol) C_{15}-C_{18} vicinal glycol, and polyoxypropylene derivates of trimethylolpropane are examples thereof.

n. Polyhydric alcohol esters. Ethylene glycol mono- and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (M.W. 200-6000) mono- and di-fatty acid esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty acid esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters are satisfactory polyhydric alcohol esters.

o. Wax esters such as beeswax, spermaceti, myristyl myristate, stearyl stearate.

p. Beeswax derivatives, e.g., polyoxyethylene sorbitol beeswax. These are reaction products of beeswax with ethoxylated

sorbitol of varying ethylene oxide content, forming a mixture of ether-esters.

q. Vegetable waxes including carnauba and candelilla waxes.

r. Phospholipids such as lecithin and derivatives.

s. Sterols. Cholesterol, cholesterol fatty acid esters are examples thereof.

t. Amides such as fatty acid amides, ethoxylated fatty acid amides, solid fatty acid alkanolamides.

The lotions further preferably comprise from 1% to 10%, more preferably from 2% to 5%, of an emulsifier. The emulsifiers can be nonionic, anionic or cationic. Examples of satisfactory nonionic emulsifiers include fatty alcohols having 10 to 20 carbon atoms, fatty alcohols having 10 to 20 carbon atoms condensed with 2 to 20 moles of ethylene oxide or propylene oxide, alkyl phenols with 6 to 12 carbon atoms in the alkyl chain condensed with 2 to 20 moles of ethylene oxide, mono- and di-fatty acid esters of ethylene oxide, mono- and di-fatty acid esters of ethylene glycol wherein the fatty acid moiety contains from 10 to 20 carbon atoms, diethylene glycol, polyethylene glycols of molecular weight 200 to 6000, propylene glycols of molecular weight 200 to 3000, glycerol, sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan and hydrophilic wax esters. Suitable anionic emulsifiers include the fatty acid soaps, e.g. sodium, potassium and triethanolamine soaps, wherein the fatty acid moiety contains from 10 to 20 carbon atoms. Other suitable anionic emulsifiers include the alkali metal, ammonium or substituted ammonium alkyl sulfates, alkyl arylsulfonates, an alkyl ethoxy ether sulfonates having 10 to 30 carbon atoms in the alkyl moiety. The alkyl ethoxy ether sulfonates contain from 1 to 50 ethylene oxide units. Satisfactory cationic emulsifiers are the quaternary ammonium, morpholinium and pyridinium compounds. Certain of the emollients described in preceding paragraphs also have emulsifying properties. When a lotion is formulated containing such an emollient, an additional emulsifier is not needed, though it can be included in the composition.

The balance of the lotion is water or a C_2 or C_3 alcohol, or a mixture of water and the alcohol. The lotions are formulated

by simply admixing all of the components together. Preferably the compound of the present invention is dissolved in the mixture. Conventional optional components can be included. One such additive is a thickening agent at a level from 1% to 10% of the composition. Examples of suitable thickening agents include: cross-linked carboxypolymethylene polymers, ethyl cellulose, polyethylene glycols, gum tragacanth, gum kharaya, xanthan gums and bentonite, hydroxyethyl cellulose, and hydroxypropyl cellulose.

2. Creams

The creams comprise an effective amount (preferably from about 0.001% to about 5%, more preferably from about 0.1% to about 1%) of a vanilloid compound; from 5% to 50%, preferably from 10% to 25%, of an emollient; the balance being water. The emollients above described can also be used in the cream compositions. Optionally the cream form contains a suitable emulsifier, as previously described. When an emulsifier is included, it is in the composition at a level from 3% to 50%, preferably from 5% to 20%.

3. Solutions

The solution form comprises an effective amount (preferably from about 0.001% to about 5%, more preferably from about 0.1% to about 1%) of a vanilloid compound; the balance being water and/or a suitable organic solvent. Suitable organic materials useful as the solvent or a part of a solvent system are as follows: propylene glycol, polyethylene glycol (M.W. 200-600), polypropylene glycol (M.W. 425-2025), glycerine, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, diethyl tartrate, butanediol, and mixtures thereof. Such solvent systems can also contain water.

These compositions in solution form can be applied to the skin as is, or else can be formulated into an aerosol and applied to the skin as a spray-on. The aerosol compositions further comprise from 25% to 80%, preferably from 30% to 50%, of a suitable propellant. Examples of such propellants are the chlorinated, fluorinated and chlorofluorinated lower molecular weight hydrocarbons. Nitrous oxide, carbon dioxide, butane, and propane are

also used as propellant gases. These propellants are used at a level sufficient to expel the contents of the container.

4. Gels

Gel compositions can be formulated by simply admixing a suitable thickening agent to the previously described solution compositions. Examples of suitable thickening agents have been previously described with respect to the lotions.

The gelled compositions comprise an effective amount (preferably from about 0.001% to about 5%, more preferably from about 0.1% to about 1%) of a vanilloid compound; from 5% to 75%, preferably from 10% to 50%, of an organic solvent as previously described; from 0.5% to 20%, preferably from 1% to 10% of the thickening agent; the balance being water.

5. Solids

Compositions of solid forms have use as stick-type compositions intended for application to the lips or other parts of the body. Such compositions comprise an effective amount (preferably from about 0.001% to about 5%, more preferably from about 0.1% to about 1%) of a vanilloid compound, and from 50% to 98%, preferably from 60% to 90%, of the previously described emollients. This composition can further comprise from 1% to 20%, preferably from 5% to 15%, of a suitable thickening agent, and optionally emulsifiers and water. Thickening agents previously described with respect to lotions are suitable herein.

Compositions used in the subject invention can be administered in a wide variety of vehicles, especially in the genital region. In addition to general skin treatment, infections in the genital area can be treated using vaginal, anal or uretheral suppositories; vaginal pessaries; vaginal or rectal tablets or inserts; catamenial and non-catamenial tampons; ointments; enemas; cones; emulsions; and douches.

Additives commonly found in topical compositions such as preservatives, e.g., methyl and ethyl-paraben, dyes and perfume can be included in any of the previously described topical compositions.

Topical compositions of the subject invention preferably comprise from about 0.1% to about 5%, more preferably from about

0.2% to about 2%, more preferably still from about 0.5% to about 1% of a vanilloid compound, and from 0% to about 10%, more preferably from about 0.2% to about 5%, more preferably still from about 0.5% to about 2% of a phosphonate antiviral compound.

EXAMPLES

The following non-limiting examples provide illustrations of various aspects of the subject invention.

Topical compositions are formulated according to Examples 1-14 by blending the listed ingredients according to conventional processes for making such compositions.

Examples 1-4

Ingredients	Example 1 (%)	Example 2 (%)	Example 3 (%)	Example 4 (%)
Capsaicin	1	1	0	0
Vanillylnonanamide	0	0	1	1
Foscarnet	0	0.25	0	0.25
Propylene glycol	55	55	55	55
Distilled water	44	43.75	44	43.75
	100	100	100	100

Examples 5-6

Ingredients	Example 5 (%)	Example 6 (%)
N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide	1	1
Foscarilate	0	0.25
Propylene glycol	97	96.75
Oleyl alcohol	2	2
	100	100

Examples 7-8

Ingredients	Example 7 (%)	Example 8 (%)
N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide	0.25	0.25
Foscarnet	0	1
Propylene glycol	30	30
Methyl laurate	5	5
Tween 20	1.67	1.67
Span 20	0.83	0.83
83 mM Lactate buffer, pH 4.5	62.25	61.25
	100	100

Examples 9-10

Ingredients	Example 9 (%)	Example 10 (%)
N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide	1	1
Foscarilate	0	5
Polyethylene glycol 300/1500 blend	99	94
	100	100

Examples 11-12

Ingredients	Example 11 (%)	Example 12 (%)
Vanillylnonanamide	1	1
Foscarnet	0	5
Cetyl alcohol	5	5
Glyceryl monostearate	15	15
Sorbitan monooleate	0.3	0.3
Polysorbate 80, USF	0.3	0.3
Methyl cellulose, 100 cps	1	1
Propyl paraben	0.2	0.2
Methyl paraben	0.2	0.2
Purified water	77	72
	100	100

Examples 13-14

Ingredients	Example 13 (%)	Example 14 (%)
N-((4-(3-phenyl-2(S)-2-amino-1-propoxy)-3-methoxyphenyl)-methyl)-nonanamide	0.25	0.25
Foscarnet	0	1
Isopropyl alcohol	30	30
Carbomer 940	1	1
Purified water	68.75	67.75
	100	100

Example 15

After a lesion episode has subsided in a person having a genital Herpes simplex infection, one gram of the topical composition of any of Examples 1, 3, 5, 7, 9, 11 or 13 is applied to the skin of the genital region for five consecutive days at the beginning of each month. The person also ingests a 500 mg capsule of acyclovir twice daily. The person remains free of the recurrence of Herpes simplex lesions.

Example 16

After a lesion episode has subsided in a person having a genital Herpes simplex infection, two grams of the topical composition of any of Examples 2, 4, 6, 8, 10, 12 or 14 is applied to the skin of the genital region for three consecutive days every two weeks. The person remains free of the recurrence of Herpes simplex lesions.

Example 17

After a lesion episode has subsided in a person having an oral Herpes simplex infection, one-half gram of the topical composition of any of Examples 1, 3, 5, 7, 9, 11 or 13 is applied to the skin of the oral region once a week. The person also ingests one 500 mg capsule of acyclovir daily. The person remains free of the recurrence of Herpes simplex lesions.

Example 18

In addition to the post lesion episode dosing of Examples 15-17, the same dosage of each composition is applied or ingested

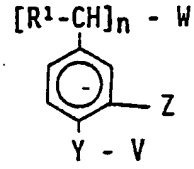
during the lesion episode, resulting in a lesion episode of less severity and shorter duration.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications to the methods and compositions disclosed herein can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

WHAT IS CLAIMED IS:

1. The use of a vanilloid compound and the use of a phosphonate antiviral compound for the manufacture of separate or combined medicaments for treating or preventing lesion episodes due to Herpes infections in a human.

2. The use of Claim 1 characterized in that the vanilloid compound has the general structure:



(1)

wherein:

(a) n is 1;

(b) -W-X- is selected from -C(O)NH- and -C(S)NH-, preferably -C(O)NH-, where either available bond of -W-X- is bonded to -R, the other being bonded to the benzyl carbom atom;

(c) $-R^1$ is selected from -H,-OH and $-CH_3$; preferably $-R^1$ is -H;

(d) -Z is selected from -H, -OH and $-OCH_3$; preferably from -OH and $-OCH_3$; more preferably -Z is $-OCH_3$;

(e) -Y- is selected from -O-, -S- and -NH-; preferably -Y- is -O-;

(f) -V is selected from -H, $-CH_3$, and $-CR^2_2-CR^2_2-NH_2$; preferably from -H and $-CH_2-CHR^2-NH_2$;

(g) $-R^2$ moieties are independently selected from hydrogen, halogen, lower alkyl, aryl, and carboxylate; or two $-R^2$ moieties are covalently bonded to form a substituted or unsubstituted alkyl, heteroalkyl, aryl, or heteroaryl ring having from about 3 to about 8 atoms in the ring including from 0 to about 3 heteroatoms; preferably from hydrogen and benzyl; and

(h) -R is saturated or mono-, di- or tri- unsaturated C_6-C_{24} straight or branched chain alkyl; preferably unsubstituted, saturated C_6-C_{14}, especially C_7-C_{10}, or mono- or di-unsaturated with double bonds C_6-C_{24}, especially mono-unsaturated cis double bond C_8-C_{14},

straight chain alkyl.

3. The use of Claim 1 or 2 characterized in that the vanilloid compound is selected from 8-methyl-N-vanillyl-6-nonenamide; N-vanillylnonanamide; N-(9-decenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-dodecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9-decenamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-tetradecenamide and N-((4-(3-phenyl-2(S)-2-amino-1-propoxy)-3-methoxyphenyl)-methyl)-nonanamide.

4. The use of Claim 1, 2 or 3 characterized in that the phosphonate antiviral compound is a phosphonoformate antiviral compound, preferably foscarnet or foscarilate.

5. The use of Claim 1 characterized in that the vanilloid compound is N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide or N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide; and the phosphonate antiviral compound is forcarnet.

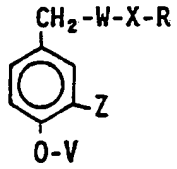
6. The use of Claim 1, 2, 3, 4 or 5 characterized in that from about 0.1 mg/kg/day to about 5 mg/kg/day of the vanilloid compound is administered, preferably topically, to the human between lesion episodes for from about 2 days to about 7 days, from about weekly to about trimonthly, and from about 0.1 mg/kg/day to about 10 mg/kg/day of the nucleoside antiviral compound is administered, preferably orally, to the human daily.

7. A topical composition comprising a safe and effective amount of a vanilloid compound, a safe and effective amount of a phosphonate antiviral compound, and a pharmaceutically-acceptable topical carrier.

8. The composition of Claim 7 wherein the composition comprises:

(a) from about 0.1% to about 5% of a vanilloid compound

having the structure



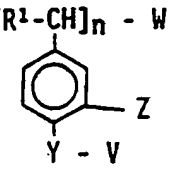
wherein -W-X- is -C(O)NH- or -NHC(O)-, -V is -H or $-CH_3$ or $-CH_2-CHR^2-NH_2$, $-R^2$ is -H or benzyl, -Z is $-OCH_3$ or -OH, and -R is unsubstituted, saturated C_6-C_{14} or mono- or di-unsaturated with double bonds C_6-C_{24} straight chain alkyl; and

(b) from about 0.1% to about 10% of a phosphonoformate antiviral compound, preferably forcarnet or foscarilate.

9. The composition of Claim 8 wherein the phosphonoformate antiviral compound is foscarnet and the vanilloid compound is N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide or N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide or N-((4-(3-phenyl-2(S)-2-amino-1-propoxy)-3-methoxyphenyl)-methyl)-nonanamide.

10. A method of treating or preventing lesion episodes due to Herpes infections in a human comprising administering to the human a combination of a safe and effective amount of a vanilloid compound and a safe and effective amount of a phosphonate antiviral compound.

11. The method of Claim 1 wherein the vanilloid compound has the general structure:



(1)

wherein:

(a) n is 1;

(b) -W-X- is selected from the group consisting of -C(O)NH- and -C(S)NH-, where either available bond of -W-X- is bonded to -R, the other being bonded to the benzyl carbom atom;

(c) $-R^1$ is selected from the group consisting of -H,-OH and $-CH_3$;

(d) -Z is selected from the group consisting of -H, -OH and $-OCH_3$;

(e) -Y- is selected from the group consisting of -O-, -S- and -NH-;

(f) -V is selected from the group consisting of -H, $-CH_3$, and $-CR^2_2-CR^2_2-NH_2$;

(g) $-R^2$ moieties are independently selected from the group consisting of hydrogen, halogen, lower alkyl, aryl, and carboxylate; or two $-R^2$ moieties are covalently bonded to form a substituted or unsubstituted alkyl, heteroalkyl, aryl, or heteroaryl ring having from about 3 to about 8 atoms in the ring including from 0 to about 3 heteroatoms; and

(h) -R is saturated or mono-, di- or tri- unsaturated C_6-C_{24} straight or branched chain alkyl.

12. The method of Claim 2 wherein $-R^1$ is -H, -W-X- is -C(O)NH-, -Y- is -O-, -V is -H or $-CH_3$, or $-CH_2-CHR^2-NH^2$, $-R^2$ is benzyl, -Z is $-OCH_3$ or -OH, and -R is unsubstituted, saturated C_6-C_{14} or mono- or di- unsaturated with double bonds C_6-C_{24} straight chain alkyl.

13. The method of Claim 3 wherein -V is -H or $-CH_2-CHR^2-NH^2$, $-R^2$ is benzyl, -Z is $-OCH_3$, and -R is saturated C_7-C_{10} or mono-unsaturated, cis double bond, C_8-C_{14}.

14. The method of Claim 4 wherein the vanilloid compound is selected from the group consisting of 8-methyl-N-vanillyl-6-nonenamide; N-vanillylnonanamide; N-(9-decenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-dodecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9-decenamide; N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide; N-((4-hydroxy-

3-methoxyphenyl)-methyl)-9Z-tetradecenamide and N-((4-(3-phenyl-2(S)-2-amino-1-propoxy)-3-methoxyphenyl)-methyl)-nonanamide.

15. The method of Claim 3 wherein the phosphonate antiviral compound is a phosphonoformate antiviral compound.

16. The method of Claim 4 wherein the phosphonate antiviral compound is foscarnet.

17. The method of Claim 5 wherein the phosphonate antiviral compound is foscarnet.

18. The method of Claim 4 wherein the phosphonate antiviral compound is a foscarilate.

19. The method of Claim 8 wherein the vanilloid compound is N-((4-hydroxy-3-methoxyphenyl)-methyl)-9Z-dodecenamide or N-(9Z-tetradecenyl)-4-hydroxy-3-methoxyphenylacetamide.

20. The method of Claim 1, 3, 7, 8 or 10 wherein from about 0.1 mg/kg/day to about 5 mg/kg/day of the vanilloid compound is administered to the human between lesion episodes for from about 2 days to about 7 days, from about weekly to about trimonthly, 0.1 mg/kg/day to about 10 mg/kg/day of the nucleoside antiviral compound is administered to the human daily.

21. The method of Claim 1, 3, 7, 8 or 10 wherein from about 0.1 mg/kg/day to about 5 mg/kg/day of the vanilloid compound is administered topically to the human between lesion episodes to tissues where lesions are likely to occur for from about 2 days to about 7 days at a frequency of from about weekly to about trimonthly, and from about 0.1 mg/kg/day to about 10 mg/kg/day of the nucleoside antiviral compound is administered perorally to the human daily.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/08678

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/66 //(A 61 K 31/66 A 61 K 31:165)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0347000 (THE PROCTER & GAMBLE CO.) 20 December 1989, see abstract (cited in the application)	1-5,7-19
A	WO,A,8302723 (BIOLOGICALS, INC.) 18 August 1983, see abstract	1-5,7-19

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19-03-1992	24.04.92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9108678 SA 54367

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0347000	20-12-89	JP-A- 2104520	17-04-90
WO-A- 8302723	18-08-83	EP-A,B 0101441	29-02-84
		US-A- 4902678	20-02-90